University of Zurich[UZH]

Zurich Open Repository and Archive
University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2003

Comment on "A pilot trial of G3139, a bcl-2 antisense oligonucleotide, and paclitaxel in patients with chemorefractory small-cell lung cancer", by C. M. Rudin et al. (Ann Oncol 2002; 13: 539-545)

Gautschi, O

DOI: https://doi.org/10.1093/annonc/mdg001

Posted at the Zurich Open Repository and Archive, University of Zurich
ZORA URL: https://doi.org/10.5167/uzh-155520
Journal Article
Published Version

Originally published at:
Gautschi, O (2003). Comment on "A pilot trial of G3139, a bcl-2 antisense oligonucleotide, and paclitaxel in patients with chemorefractory small-cell lung cancer", by C. M. Rudin et al. (Ann Oncol 2002; 13: 539-545). Annals of Oncology, 14(1):170.
DOI: https://doi.org/10.1093/annonc/mdg001

Annals of Oncology 14: 170, 2003

Comment on "A pilot trial of G3139, a *bcl-2* antisense oligonucleotide, and paclitaxel in patients with chemorefractory small-cell lung cancer", by C. M. Rudin et al. (Ann Oncol 2002; 13: 539–545)

In their pilot study, Rudin et al. describe the safety, feasibility and toxicity profile of the combination of paclitaxel and G3139 (Genasense™), a *bcl-2* antisense oligonucleotide, in patients with chemoresistant small-cell lung cancer (SCLC). Tolerance of G3139 in these patients was good and further studies are ongoing.

Although 'proof of principle' was not the aim of the study, and because repeated tumor biopsy for the measurement of target protein expression in tumor cells was not possible, bcl-2 protein expression was measured in peripheral-blood mononuclear cells (PBMCs) before and after the administration of G3139. A decrease in bcl-2 protein in PBMCs may prove sustained biological activity upon G3139 i.v. infusion, however, it is not an accurate substitute for bcl-2 expression in tumor cells, and therefore, no conclusions should be drawn from these results. We believe that, when studying antisense activity, analysis of the tumor cells must remain the gold-standard for target validation as long as no surrogate markers are available. It is especially necessary to evaluate potential surrogate markers, such as circulating tumor-specific protein, DNA and mRNA, for clinical studies of patients with tumors that are not readily accessible.

Another concern arises from the fact that untreated, as well as chemoresistant, SCLC cells express not only bcl-2 but also bcl-xL, another potent anti-apoptotic protein, at remarkably high levels [1]. Furthermore, tumor cells are able to switch expression from bcl-2 to bcl-xL [2], resulting in sustained tumor cell survival. In order to adequately address this complication, we have developed a single 'bispecific' antisense oligonucleotide that simultaneously targets the *bcl-2* and *bcl-xL* mRNA. This compound has demonstrated inhibition of target protein expression, as well as potent antitumor efficacy, in preclinical models of various human tumors *in vitro* and *in vivo* [3].

The publication by Rudin et al. is an important step towards the broad therapeutic use of antisense oligonucleotides against malignant human tumors; we anticipate new challenges will arise when more of these promising compounds are carried from the bench to the clinic.

O. Gautschi[1]*, U. Zangemeister-Wittke[2] & R. A. Stahel[2]

[1]Institute of Medical Oncology, University Hospital, Bern;
[2]Division of Medical Oncology, University Hospital, Zürich, Switzerland
(*E-mail: oliver.gautschi@insel.ch)

References

1. Reeve JG, Xiong J, Morgan J, Bleehen NM. Expression of apoptosis-regulatory genes in lung tumour cell lines: relationship to p53 expression and relevance to acquired drug resistance. Br J Cancer 1996; 73: 1193–1200.
2. Han Z, Chatterjee D, Early J et al. Isolation and characterization of an apoptosis-resistant variant of human leukemia HL-60 cells that has switched expression from Bcl-2 to Bcl-xL. Cancer Res 1996; 56: 1621–1628.
3. Gautschi O, Tschopp S, Olie RA et al. Activity of a novel bcl-2/bcl-xL-bispecific antisense oligonucleotide against tumors of diverse histologic origins. J Natl Cancer Inst 2001; 93: 463–471.

DOI: 10.1093/annonc/mdg001

© 2003 European Society for Medical Oncology